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(54) Title: USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF, INTER ALIA, NEUROPATHIC PAIN AND COLON CANCER

(57) Abstract: The present invention relates to the use of an EP4 receptor ligand in the manufacture of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine, and for increasing the latency of HIV infection.

Use of EP4 Receptor Ligands in the Treatment of, *inter alia*, Neuropathic Pain and Colon Cancer

The present invention relates to new uses for EP4 receptor ligands.

The EP4 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP1, EP2 and EP3).

Compounds exhibiting EP4 binding activity have been described in, for example, WO00/18744, WO00/03980, WO00/15608, WO00/16760, WO00/21532, WO98/55468, EP0855389 and EP0985663. GB2330307 describes the use of EP4 antagonists in the treatment of conditions with accelerated bone resorption.

It has now been found that EP4 receptor ligands are of use in the treatment of neuropathic pain, colon cancer, migraine and in increasing the latency of HIV infection.

It is believed that selective EP4 receptor ligands exhibit a number of advantages over current non-steroidal anti-inflammatory (NSAID) and cyclo-oxygenase-2 inhibitor (COX-2i) drugs which act via a number of prostaglandin pathways. By selectively binding to the EP4 receptor, the beneficial activities of other prostaglandin pathways are retained. The use according to the instant invention therefore provides greater efficacy and improved gastro-intestinal safety over NSAIDs.

The present invention provides the novel use of an EP4 receptor ligand in the manufacture of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine and for increasing the latency of HIV infection.

In a further aspect the invention provides a novel method of increasing the latency of HIV infection; and for treating migraine, neuropathic pain, and colon cancer; in a mammal, including man, comprising administration of an effective amount of an EP4 receptor ligand.

In a further aspect the present invention provides the novel use of an EP4 receptor antagonist in the manufacture of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine and for increasing the latency of HIV infection.

In a further aspect the invention provides a novel method of increasing the latency of HIV infection; and for treating migraine, neuropathic pain, and colon cancer; in a mammal, including man, comprising administration of an effective amount of an EP4 receptor antagonist.

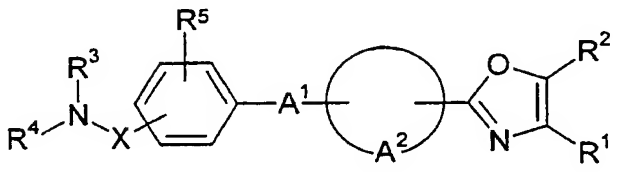
It is to be understood that reference to treatment as used herein includes treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

Suitable EP4 receptor ligands for use in the present invention include those described in GB2330307, WO00/18744, WO00/03980, WO00/15608, WO00/16760, WO00/21532, WO98/55468, EP0855389 and EP0985663, all incorporated by reference herein. A preferred EP4 receptor ligand for use in the present invention is the compound [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid and pharmaceutically acceptable derivatives thereof of formula (IF) below.

Compounds described in GB2330307 are [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof and [1R[1α(Z),2β,5α]]-(-)-7-[5-[[1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof.

[1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof and [1R[1α(Z),2β,5α]]-(-)-7-[5-[[1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof may be prepared and formulated according to the methods described in UK Patent Application No GB 2075503.

Compounds described in WO00/18744 are oxazole compounds of formula (I)



(I)

wherein

R^1 is aryl which may be substituted with halogen(s),

R^2 is aryl which may be substituted with halogen(s),

X is single bond, C=O or SO_2,

R^3 and R^4 are independently hydrogen or suitable substituent,

(wherein X is C=O, neither R^3 nor R^4 is hydrogen),

R^3 and R^4 may be linked together to form -N◯

-N◯ is N-containing heterocyclic group which may be substituted with one or more suitable substituent(s),

R^5 is

(1) hydrogen,

(2) hydroxy,

(3) carboxy, or

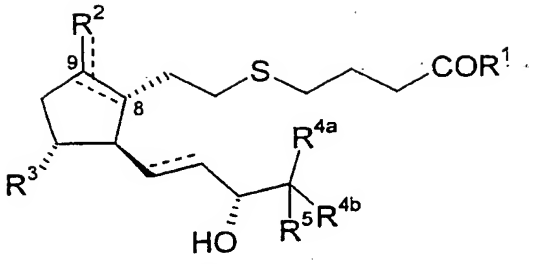
(4) protected carboxy,

A^1 is lower alkylene or single bond,

◯A^2 is cyclo (C_3 - C_9) alkane or cyclo (C_5 - C_9)alkene,

or a pro-drug thereof, or a pharmaceuticially acceptable salt thereof; which may be prepared according to the method described therein.

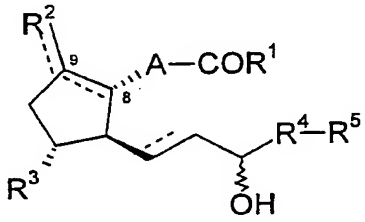
Compounds described in WO00/03980 are 5-thia-ω-substituted phenyl-prostaglandin E derivatives of formula (IA)



(IA)

wherein each symbol is as defined in the specification.

Compounds described in WO00/15608 are ω-substituted phenyl-prostaglandin E derivatives of formula (IB)



(IB)

wherein each symbol is as defined in the specification.

Compounds described in WO00/21532 are
5-butyl-2,4-dihydro-4-[[2'-[N-(3-chloro-2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one potassium salt,

5-butyl-2,4-dihydro-4-[[2'-[N-(2-methyl-3-furoyl)sulfamoyl]biphenyl4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,

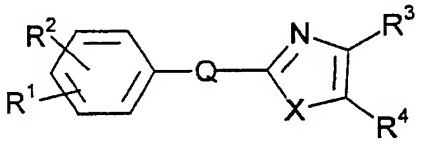
5-butyl-2,4-dihydro-4-[[2'-[N-(3-methyl-2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,

5-butyl-2,4-dihydro-4-[[2'-[N-(2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[(2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,

5-butyl-2,4-dihydro-4-[[2'-[N-[2-(methylpyrrole)carbonyl]sulfamoyl]biphenyl-4-yl]methyl]-2-[(2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,

and the pharmaceutically acceptable salts thereof, and mixtures thereof.

Compounds described in WO98/55468 are azole compounds of formula (IC):



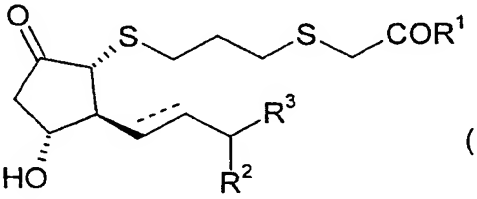
(IC)

wherein R^1 is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; hydroxy; halo(lower)alkylsulfonyloxy; lower alkoxy optionally substituted with hydroxy or carbamoyl; aryl substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,
R^2 is hydrogen or lower alkyl,
R^3 is aryl optionally substituted with halogen,
R^4 is aryl optionally substituted with halogen,

Q is $-A^1-\overset{A^2}{\bigcirc}-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene,

$\overset{A^2}{\bigcirc}$ is cyclo $(C_5\text{-}C_9)$alkene, cyclo $(C_3\text{-}C_9)$alkane, bicyclo$(C_6\text{-}C_9)$alkene or bicyclo $(C_5\text{-}C_9)$alkane, and $-A^3-$ is a single bond or lower alkylene], and
X is O, NH or S; which may be prepared according to the methods described therein.

Compounds described in EP0855389 are 3,7-dithiaprostanoic acid derivatives of the formula (ID):



(ID)

(wherein R^1 is hydroxy, C1-4alkoxy or a group of the formula:

$-NR^6R^7$

wherein R^6 and R^7, independently, are hydrogen atom or C1-4alkyl,

R^2 is hydrogen atom or hydroxy,

R^3 is

(i) C1-8alkyl, C2-8alkenyl or C2-8alkynyl,

(ii) phenyl or C3-7cycloalkyl,

(iii) C1-8alkyl, C2-8alkenyl or C2-8alkynyl substituted by phenyl or C3-7cycloalkyl,

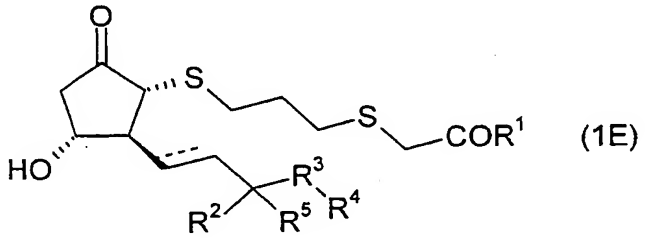
with the provisio that alkyl, alkenyl, alkynyl in (i) or (iii) may be substituted by one hydroxy group, when R^2 is hydrogen atom;

the symbol ---- is a double or single bond;

the formula including the 8-epi equilibrium compound thereof);

a non-toxic salt thereof or a cyclodextrin clathrate thereof, which may be prepared according to the methods described therein.

Compounds described in EP0985663 are 3,7-dithiaprostanoic acid derivatives of the formula (IE)



(1E)

wherein R^1 is hydroxy, C1-6 alkyloxy or a group of the formula:

NR^6R^7

(in which R^6 and R^7 are independently hydrogen or C1-6 alkyl);

R^2 is hydrogen or hydroxy;

R^3 is single bond or C1-6 alkylene;

R^4 is

(i) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1 to 3 substituents selected from C1-6 alkyloxy and halogen atom(s),

(ii) phenyloxy or C3-7 cycloalkyloxy,

(iii) furyl, furyloxy, thienyl, thienyloxy, naphthyl, naphthyloxy, phthalanyl or phthalanyloxy,

(iv) phenyl, phenyloxy, C3-7 cycloalkyl or C3-7 cycloalkyloxy substituted by 1 to 3 substituents selected from the following groups:

C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkyloxy, C1-6 alkyloxy-C1-6 alkyl, C1-6 alkyloxy-C1-6 alkyloxy, C2-6 alkenyloxy-C1-6 alkyl, C1-6 alkyl substituted by 1 to 3 of hydroxy, C1-6 alkyl substituted by 1 to 3 of halogen atom(s), C1-6 alkylthio, C1-6 alkylthio-C1-6 alkyl, C1-6 alkylthio-C1-6 alkyloxy, C2-6 alkenylthio-C1-6 alkyl, C1-6 alkylsulfonyl, halogen, trihalomethyl, cyano, nitro, amino, hydroxy, C3-7 cycloalkyl, C3-7 cycloalkyloxy, C3-7 cycloalkyl-C1-6 alkyl, C3-7 cycloalkyloxy-C1-6 alkyl, phenyl, phenyloxy, phenyl-C1-6 alkyl, phenyl-C2-6 alkenyl, phenyl-C2-6 alkynyl, phenyloxy-C1-6 alkyl, phenyloxy-C2-6 alkenyl, phenyloxy-C2-6 alkynyl, furyl, furyloxy, furyl-C1-6 alkyl, furyloxy-C1-6 alkyl, thienyl, thienyloxy, thienyl-C1-6 alkyl and thienyloxy-C1-6 alkyl

(the above mentioned phenyl, furyl, thienyl and cycloalkyl being optionally substituted by 1 to 3 substituents selected from C1-6 alkyl, C1-6 alkyloxy, C1-6 alkyloxy-C1-6 alkyl, nitro, halogen, trihalomethyl, amino and hydroxy), or

(v) furyl, furyloxy, thienyl, thienyloxy, naphthy, naphthyloxy, phthalanyl or phthalanyloxy substituted by 1 to 3 substituents selected from the following groups:

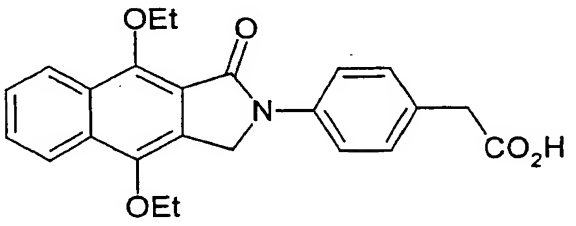
C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkyloxy, C1-6 alkyloxy-C1-6 alkyl, C1-6 alkyloxy-C1-6 alkyloxy, C2-6 alkenyloxy-C1-6 alkyl, C1-6 alkyl substituted by 1 to 3 of hydroxy, C1-6 alkyl substituted by 1 to 3 of halogen atom(s), C1-6 alkylthio, C1-6 alkylthio-C1-6 alkyl, C1-6 alkylthio-C1-6 alkyloxy, C2-6 alkenylthio-C1-6 alkyl, C1-6 alkylsulfonyl, halogen, trihalomethyl, cyano, nitro, amino, hydroxy, C3-7 cycloalkyl, C3-7 cycloalkyloxy, C3-7 cycloalkyl-C1-6 alkyl, C3-7 cycloalkyloxy-C1-6 alkyl, phenyl, phenyloxy, phenyl-C1-6 alkyl, phenyl-C2-6 alkenyl, phenyl-C2-6 alkynyl, phenyloxy-C1-6 alkyl, phenyloxy-C2-6 alkenyl.

phenyloxy-C2-6 alkynyl, furyl, furyloxy, furyl-C1-6 alkyl, furyloxy-C1-6 alkyl, thienyl, thienyloxy, thienyl-C1-6 alkyl and thienyloxy-C1-6 alkyl
(the above mentioned phenyl, furyl, thienyl and cycloalkyl being optionally substituted by 1 to 3 substituents selected from C1-6 alkyl, C1-6 alkyloxy, C1-6 alkyloxy-C1-6 alkyl, nitro, halogen, trihalomethyl, amino and hydroxy);

R^5 is hydrogen or C1-6 alkyl;

and the symbol ---- is double bond or single bond;
the formula including the 8-epi equilibrium compound;
with the proviso that when R^2 is hydrogen, C1-6 alkylene represented by R^3 may be substituted by a hydroxy group;
or a non-toxic salt thereof or cyclodextrin clathrate thereof, which may be prepared according to the methods described therein.

As mentioned above, a preferred EP4 receptor ligand for use in the present invention is the compound [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid of formula (IF) below.



(IF)

The compound of formula (IF) and pharmaceutically acceptable derivatives thereof is novel and therefore forms a further feature of the invention.

The ability of the compounds to bind to EP4 receptors may be demonstrated in the Human EP_4 Scintillation Proximity Assay.

Quantification of radioligand binding by scintillation proximity assay (SPA) is a long-established principle. Briefly, the affinity of compounds for a receptor is assessed by the specific competition between known quantities of radiolabelled

ligand and compound for that receptor. Increasing concentrations of compound reduce the amount of radiolabel that binds to the receptor. This gives rise to a diminishing scintillation signal from SPA beads coated with membranes that bear the receptor. The signal may be detected with a suitable scintillation counter and the data generated may be analysed with suitable curve-fitting software.

The human EP_4 SPA assay (hereafter referred to as 'the assay') utilises membranes prepared from Chinese Hamster Ovary (CHO cells) infected with Semliki Forest Virus (SFV). The virus is previously transfected with an SFV-1 RNA construct containing the hEP_4 receptor. Cells washed free of media are homogenised in a pH-buffered medium containing peptidase inhibitors. A suitable buffer is of the following composition: 50mM HEPES, 1mM EDTA, 25μg/ml bacitracin, 100μM leupeptin, 1mM PMSF, 2μM Pepstatin A, pH adjusted to 7.4 with KOH. Following removal of cell debris by a low-speed centrifugation, a pellet of membranes is prepared by a high-speed (48000g) centrifugation of the resulting supernatant. Membrane suspensions such as that described may be stored at -80°C until used.

For assay, membranes expressing human EP_4 receptors are diluted in a pH-buffered medium and mixed with SPA beads coated with a suitable substance to facilitate the adhesion of membranes to the beads. The concentrations of membrane protein and SPA beads chosen should result in SPA binding signal of at least 300 corrected counts per minute (CCPM) when tritiated radioligand at a concentration close to its K_d (affinity value) is combined with the mixture. Non-specific binding (nsb) may be determined by competition between the radiolabelled ligand and a saturating concentration of unlabelled ligand. In order to quantify the affinity of EP4 receptor ligands, compounds are diluted in a stepwise manner across the wells of a 96-well plate. Radioligand, compound, and unlabelled ligand are then added to a 96-well plate suitable for the measurement of SPA binding signals prior to the addition of bead / membrane mixture to initiate the binding reaction. Equilibrium may be achieved by incubation at room temperature for 120 minutes prior to scintillation counting. The data so generated may be analysed by means of a computerised curve-fitting routine in order to quantify the concentration of compound that displaces 50% of the specific radioligand binding (IC_{50}). The affinity (pK_i) of the compound

may be calculated from the IC_{50} by application of the Cheng-Prusoff correction. Suitable reagents and protocols are: reaction buffer containing 50mM HEPES, 10mM $MgCl_2$, pH adjusted to 7.4 with KOH; SPA beads coated with wheatgerm agglutinin; 1.25nM [^{3}H]-prostaglandin E_2 as radioligand; 10μM prostaglandin E_2 as unlabelled ligand; a three-fold dilution series of compound starting at 10μM and ending at 0.3nM is adequate.

By application of this technique, 4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid (IF) had a pKi of 7.00 ± 0.28 (mean ± standard deviation of the mean; n = 87).

The novel use of EP4 receptor ligands in the treatment of neuropathic pain has been demonstrated in the following test.

The chronic constriction injury (CCI) model was used to induce the neuropathic hypersensitivity (Bennett & Xie, 1988) in male random hooded rats.

Under isoflurane anaesthesia, the common left sciatic nerve was exposed at mid thigh level and four loose ligatures of Chromic gut tied around it. The wound was then closed and secured using suture clips. The surgical procedure was identical for the sham operated animals except the sciatic nerve was not ligated. The rats were allowed a period of seven days to recover from the surgery before behavioural testing began.

4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid (IF) (10mgkg-1 b.i.d. PO) was dosed chronically for 14 days (days 20-33 post-operative). A reversal of the CCI-induced decrease in paw withdrawal threshold became apparent following 3 days of chronic dosing which was maximal after 1 week. This reversal was maintained throughout the remainder of the dosing period. Following cessation of the drug treatment the paw withdrawal threshold returned to that of the vehicle treated CCI-operated animals.

The compounds for use in the invention may be administered orally at a dose of from 0.1 to 10 mg/kg body weight per day and more particularly 0.3 to 3 mg/kg body weight per day, calculated as the free base. The dose range for adult

human beings is generally from 8 to 1000 mg/day, such as from 35 to 800 mg/day, preferably 20 to 200 mg/day, calculated as the free base.

The precise amount of the compounds administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend upon a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

The compounds and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

While it is possible for the compounds to be administered as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The formulations comprise the compounds together with one or more acceptable carriers or diluents therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the compounds ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets (e.g. chewable tablets in particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured

basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

The compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The EP4 receptor ligand for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib or parecoxib; 5-lipoxygenase inhibitors; low dose aspirin; NSAID's, such as diclofenac, indomethacin or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine 1 agonists; recombinant human TNF receptor fusion proteins such as etanercept; sodium channel antagonists, such as lamotrigene; NMDA antagonists, such as glycine antagonists; and $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, the use of a combination comprising an EP4 receptor ligand with a further therapeutic agent in the treatment of migraine, neuropathic pain, colon cancer and in increasing the latency of HIV infection.

In a further aspect, the invention provides the use of a combination comprising an EP4 receptor antagonist with a further therapeutic agent in the treatment of

migraine, neuropathic pain, colon cancer and in increasing the latency of HIV infection.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When an EP4 receptor ligand is used in combination with a second therapeutic agent active against the same disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

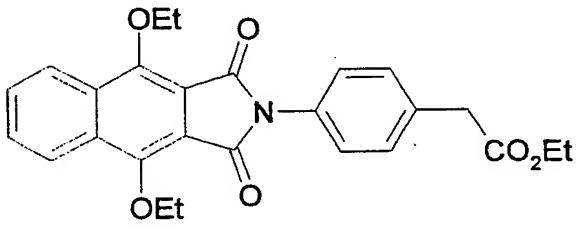
Likewise, when an EP4 receptor antagonist is used in combination with a second therapeutic agent active against the same disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Preferred unit dosage formulations are those containing an effective daily dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient. Conveniently that may be from 5 mg to 1000 mg, such as from 8 mg to 1000 mg, more conveniently 35 mg to 800 mg, and most conveniently 20 to 200 mg, calculated as the free base.

The compound of formula (IF) and pharmaceutically acceptable derivatives thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure.

A suitable method for the preparation of compound (IF) and pharmaceutically acceptable derivatives thereof is described below and forms a further aspect of the invention.

Compound (IF) may be prepared by reducing the compound



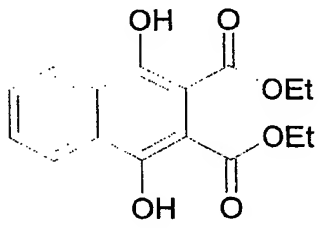
with a suitable reducing agent, for example zinc in acetic acid at elevated temperature, followed by separation of isomers and deprotection (eg. with aqueous base at elevated temperature).

The following Example which should not be construed as constituting a limitation thereto is provided to illustrate the invention.

^{1}H NMR spectra were obtained at 400MHz on a Bruker DPX400 spectrophotometer. J values are given in Hz. Mass spectra were obtained on a Micromass series II MS (electrospray positive or negative).

Intermediate 1

Ethyl 1,4-dihydroxy- 2,3-naphthalenedicarboxylate

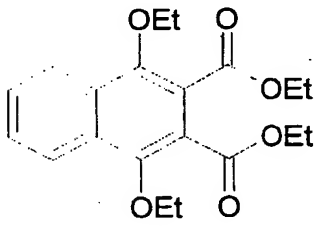


Sodium (60g, 2.6mol) was dissolved in ethanol (1.2L) and the mixture was cooled to 40°C. Diethylphthalate (960ml, 4.83mol) was added and the mixture heated under nitrogen until the temperature reached 115°C. Diethyl succinate (211.3g, 1.21mol) was added dropwise over 45 min. The reaction was heated at 115°C for a further 45 min, cooled to room temperature and poured onto water

(1.2L). Ethyl acetate (1L) was added and stirred, the layers were separated and the organics were extracted with sodium hydroxide solution (2N, 1L). The combined aqueous was acidified to pH 3 and the mixture extracted with ethyl acetate (2 x 1L). The combined organics were washed with a saturated solution of sodium hydrogen carbonate (2 x 1.5L), then brine, dried ($MgSO_4$), filtered and the solvent evaporated under vacuum. The residue was purified using a 2.5kg Biotage column eluting with 5% ethyl acetate / hexane to give ethyl 1,4-dihydroxy- 2,3-naphthalenedicarboxylate as a white solid, (60g, 16%)
δH $CDCl_3$ 10.44,(2H, s), 8.34,(2H, m), 7.68,(2H, m), 4.37,(4H, q), 1.37,(6H, t).

Intermediate 2

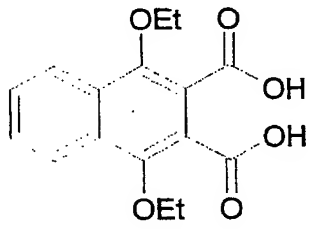
Ethyl 1,4-diethoxy- 2,3-naphthalenedicarboxylate



Ethyl 1,4-dihydroxy- 2,3-naphthalenedicarboxylate (30g, 98.6 mmol) and potassium carbonate (150g, 1.09mmol) were stirred in acetone (600ml) under nitrogen. Iodoethane (150g, 0.96mol) was added and the mixture was stirred at reflux overnight. The reaction was cooled, diluted with ethyl acetate and filtered. The filtrate was evaporated to leave a brown oil, which was dissolved in toluene and washed with potassium hydroxide solution (5%, 150ml) and brine. Drying over magnesium sulphate and evaporation of the solvent gave a yellow solid. Purification using an 800g Biotage column gave ethyl 1,4-diethoxy- 2,3-naphthalenedicarboxylate as a white solid (32g, 90%).
δH $CDCl_3$ 8.16,(2H, m), 7.60,(2H, m), 4.40,(4H, q), 4.18,(4H, q), 1.50,(6H, t), 1.40,(6H, t).

Intermediate 3

1,4-Diethoxy- 2,3-naphthalenedicarboxylic acid

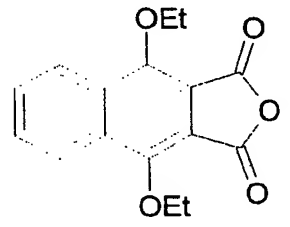


Ethyl 1,4-diethoxy- 2,3-naphthalenedicarboxylate (32g, 89mmol) was added to a solution of sodium hydroxide (20g) in ethanol (200ml) and water (40ml) and stirred for 1.5h at 60°C. The reaction was cooled and the thick white suspension was filtered. The solid was dissolved in a mixture of ethyl acetate (200ml) and water (800ml). The layers were separated and the aqueous was acidified with hydrochloric acid (2M, 120ml). The aqueous was extracted with ethyl acetate (2x) and the combined organics were dried ($MgSO_4$). Evaporation of the solvent under vacuum gave 1,4-diethoxy- 2,3-naphthalenedicarboxylic acid as a white solid (25g, 92%).

δH [$^2H_6$] – DMSO 13.26,(2H, s), 8.15,(2H, m), 7.72,(2H, m), 4.13,(4H, q), 1.42,(6H, t).

Intermediate 4

1,4-Diethoxy- 2,3-naphthalenedicarboxylic anhydride

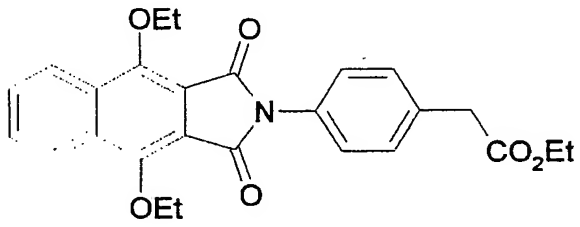


1,4-Diethoxy- 2,3-naphthalenedicarboxylic acid (25g, 82mmol) was added to a solution of thionyl chloride (23.3g) in chloroform (150ml) and stirred at reflux for 1h. The resulting solution was cooled and evaporated to dryness. Further chloroform was added and evaporation repeated to give 1,4-diethoxy- 2,3-naphthalenedicarboxylic anhydride as a yellow solid (23.3g, 99%).

δH [$^2H_6$] – DMSO 8.42,(2H, m), 7.93,(2H, m), 4.53,(4H, q), 1.46,(6H, t).

Intermediate 5

Ethyl[4-(4,9-diethoxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate

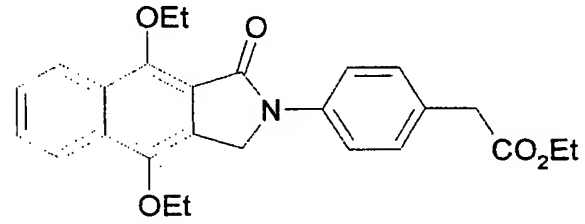


1,4-Diethoxy- 2,3-naphthalenedicarboxylic anhydride (23.3g, 81.5mmol) and ethyl (4-aminophenyl)acetate (14.8g, 82mmol) were refluxed under nitrogen in acetic acid (160ml) overnight. The mixture was cooled to room temperature and poured into water (1L). The white solid was filtered, washed with water and dissolved in dichloromethane (800ml). The solution was washed with water, brine and dried ($MgSO_4$) and the solvent evaporated under vacuum to give ethyl [4-(4,9-diethoxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate as an off-white solid (33g, 96%).

δH [$^2H_6$] – DMSO 8.40,(2H, m), 7.87,(2H, m), 7.42,(4H, s), 4.47,(4H, q), 4.12,(2H, q), 3.76,(2H, s), 1.45,(6H, t), 1.21,(3H, t).

Example 1 – Step 1

Ethyl [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate



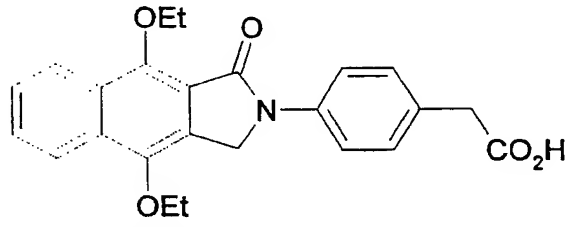
Ethyl [4-(4,9-diethoxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate (33g, 73mmol) and zinc (90g, 1.38mol) were refluxed in acetic acid for 66h. An additional quantity of zinc (25g, 0.38mol) was added and reflux

continued for 18h. The mixture was filtered hot and the filtrate was evaporated to a yellow solid. The solid was purified by 800g Biotage column eluting with 20% ethyl acetate/ hexane to give a white solid, which was triturated in ether to give a white solid. A further fraction was obtained by crystallisation from the ether residues. A total of 10.2g, 32% of ethyl [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate was obtained.

δH $CDCl_3$ 8.42,(1H, d), 8.18,(1H, d), 7.88,(2H, d), 7.63,(2H, m), 7.38,(2H, d), 5.00,(2H, s), 4.51,(2H, q), 4.26,(2H, q), 4.18,(2H, q), 3.65,(2H, s), 1.57,(6H, m), 1.28,(3H, t).

Example 1 – Step 2

[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid



Ethyl [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate (5.86g, 13.5mmol) and potassium carbonate (12g) were added to a mixture of ethanol (146ml) and water (70ml) and heated to reflux for 2h. The solution was cooled to room temperature and the solvent evaporated under vacuum to leave an off-white solid. The solid was slurried in water and the water was evaporated under vacuum. The residue was stirred in hydrochloric acid (2N) for 2h, filtered and washed with water. Drying of the solid at 40° C in a vacuum oven gave [4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid as a white solid (4.5g, 82%)

δH [$^2H_6$] – DMSO 12.27,(1H, b), 8.25,(1H, d), 8.12,(1H, d), 7.86,(2H, d), 7.61,(2H, m), 7.27,(2H, d), 5.10,(2H, s), 4.34,(2H, q), 4.25,(2H, q), 3.54,(2H, s), 1.41,(3H, t), 1.37,(3H, t). MS 406, [MH^+]

Claims:

1. The use of an EP4 receptor ligand in the manufacture of a medicament for the treatment of neuropathic pain.

2. The use of an EP4 receptor ligand in the manufacture of a medicament for the treatment of colon cancer.

3. The use of an EP4 receptor ligand according to claims 1 or 2 wherein the EP4 receptor ligand is combined with one or more further therapeutic agents.

4. The use of an EP4 receptor ligand according to claim 3 wherein the therapeutic agents may be any of: a COX-2 inhibitor, a 5-lipoxygenase inhibitor, low dose aspirin, NSAID's, a leukotriene receptor antagonist, DMARD's, an adenosine 1 agonist, a recombinant human TNF receptor fusion protein, a sodium channel antagonist, an NMDA antagonist, and a 5HT1 agonist.

5. A method of treating neuropathic pain in a mammal, including man, comprising administration of an effective amount of an EP4 receptor ligand.

6. A method of treating colon cancer in a mammal, including man, comprising administration of an effective amount of an EP4 receptor ligand.

7. A pharmaceutical composition comprising an EP4 receptor ligand for use in the treatment of neuropathic pain.

8. A pharmaceutical composition comprising an EP4 receptor ligand for use in the treatment of colon cancer.

9. A pharmaceutical composition comprising an EP4 receptor ligand and a COX-2 inhibitor, in combination with a pharmaceutically acceptable carrier.

10. The use of an EP4 receptor antagonist in the manufacture of a medicament for the treatment of neuropathic pain.

11. The use of an EP4 receptor antagonist in the manufacture of a medicament for the treatment of colon cancer.

12. The use of an EP4 receptor antagonist according to claims 10 or 11 wherein the EP4 receptor antagonist is combined with one or more further therapeutic agents.

13. The use of an EP4 receptor antagonist according to claim 12 wherein the therapeutic agents may be any of: a COX-2 inhibitor, a 5-lipoxygenase inhibitor, low dose aspirin, NSAID's, a leukotriene receptor antagonist, DMARD's, an adenosine 1 agonist, a recombinant human TNF receptor fusion protein, a sodium channel antagonist, an NMDA antagonist, and a 5HT1 agonist.

14. A method of treating neuropathic pain in a mammal, including man, comprising administration of an effective amount of an EP4 receptor antagonist.

15. A method of treating colon cancer in a mammal, including man, comprising administration of an effective amount of an EP4 receptor antagonist.

16. A pharmaceutical composition comprising an EP4 receptor antagonist for use in the treatment of neuropathic pain.

17. A pharmaceutical composition comprising an EP4 receptor antagonist for use in the treatment of colon cancer.

18. A pharmaceutical composition comprising an EP4 receptor antagonist and a COX-2 inhibitor, in combination with a pharmaceutically acceptable carrier.

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Published:
— *with international search report*

(88) Date of publication of the international search report:
20 December 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF NEUROPATHIC PAIN AND COLON CANCER

(57) Abstract: The present invention relates to the use of an EP4 receptor ligand in the manufacture of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine, and for increasing the latency of HIV infection.

WO 01/10426 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07669

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4035 A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 330 307 A (GLAXO GROUP LTD) 21 April 1999 (1999-04-21) page 1, line 1 - line 31 ---	7,9,16, 18
X	US 4 327 092 A (COLLINGTON ERIC W ET AL) 27 April 1982 (1982-04-27) page 1, paragraph 1 - paragraph 3 column 2, paragraph 49 - paragraph 57 ---	7,9,16, 18
A	EP 0 520 573 A (GLAXO INC) 30 December 1992 (1992-12-30) page 3; figure II --- -/--	1,3-5,7, 9,10, 12-14, 16,18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2001	16.07.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07669

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 501 579 A (MERCK FROSST CANADA INC) 2 September 1992 (1992-09-02) page 5, line 66 -page 6, line 13 page 4; figure 1 ---	1,3-5,7, 9,10, 12-14, 16,18
A	US 5 834 463 A (KATO KOICHI ET AL) 10 November 1998 (1998-11-10) example 75 column 1, paragraph 7 -----	1,3-5,7, 9,10, 12-14, 16,18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/07669

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,3-4 (partially),5,7,9-10,12-13 (partially),14,16,18

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,3-4 (partially),5,7,9-10,12-13 (partially),14,16, 18

   Use of ep4 ligands for treating neuropathic pain.

2. Claims: 2,3-4(partially),6,8,11,12-13(partially),15,17

   Use of ep4 ligands for treating colon cancer.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 3.

Although claims 5,14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

Present claims 1,3-5,7-10,12-14,16-18 relate to a compound defined by reference to a desirable characteristic or property, namely the capacity of binding the receptor EP4, as a ligand or antagonist.
Present claims 4,18 relate to compounds defined by reference to a desirable characteristic or property, namely the activity as COX-2 inhibitors, as 5-lipoxygenase inhibitors, as NSAID, as leukotriene receptor antagonists, as DMARD, as adenosine 1 agonists, as recombinant human TNF receptor fusion protein, as sodium channel antagonist, as NMDA antagonists and as 5HT1 agonists.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in examples at pages 15-19.

Claims searched completely: none.
Claims searched incompletely: 1,3-5,7-10,12-14,16-18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/07669

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